8

Efficacy of Aliskiren/Hydrochlorothiazide Combination for the Treatment of Hypertension: A Meta-Analytical Revision

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1. Introduction

Hypertension is a major risk factor in the development of cardiovascular disease, with myocardial infarction, stroke and renal failure being one of the most important health problems worldwide due to its high prevalence and deleterious impact on the population in terms of excessive morbidity and mortality. Currently, hypertension is estimated to affect approximately 30% of the US and European population and 1 thousand million people worldwide and, as the population ages, this number is expected to increase even further (Wolf-Maier et al., 2003; Kearney et al., 2005; Yoon et al., 2010). Moreover, despite advances in treatment of the condition, hypertension control rates continue to be suboptimal in both the US and Europe as only about one third have their blood pressure (BP) reduced to the recommended levels by the 7th Joint National Committee (JNC-7) to under 140/90 mm Hg for uncomplicated hypertension, and less than 130/80 mmHg for those with diabetes mellitus or renal disease (Chobanian et al., 2003).

Hypertension is a controllable disease and effective pharmacological therapies have been available for nearly 50 years. Socio-economic conditions, medication non-adherence, inadequate prevention strategies and resistant hypertension have all been implicated as barriers to adequate BP control. The major pharmacological strategies currently used for hypertension management include volume control with diuretics, suppression of central and peripheral sympathetic nervous system activity with beta-blockers and alfa-blockers, vasodilation with ion channel manipulation and blockade of renin-angiotensin-aldosterone system (RAAS). Since monotherapy controls the BP of less than 50% of treated hypertensive patients (Materson et al., 1993; Cushman et al., 2002), combination therapy with two or more antihypertensive medications with complementary mechanisms is often required to achieve BP control to recommended levels (Chobanian et al., 2003; Mancia et al., 2007). At present, the most widely used antihypertensive combinations involve hydrochlorothiazide (HCTZ) and drugs that block the RAAS, such as angiotensin-converting enzyme (ACE) inhibitors and angiotensin II type-1 receptor blockers (ARBs).

Recently a new blocker of the RAAS, aliskiren, has been developed and approved by the US Food and Drug Administration (FDA, on 5th March 2007) and by the European Medicines Agency (EMEA, on 22nd August 2007) for the treatment of essential hypertension. Aliskiren is an oral direct renin inhibitor, the rate-limiting enzyme in the production of the end product of the RAAS cascade, angiotensin II (Ang II), a potent vasoactive peptide. Aliskiren is a long-acting antihypertensive (half-life ≈ 40 hours) and has been shown in several clinical trials to be effective in lowering BP, safe and well tolerated in daily doses of 150 and 300 mg (approved once-daily doses) (Musini et al., 2009). In a recent systematic review and meta-analysis of six double-blind randomized clinical trials to quantify the systolic and diastolic BP (SBP and DBP) lowering efficacy of aliskiren in the treatment of adults with essential hypertension, the obtained weighted mean differences with 95% CI (confidence interval) were: aliskiren 150 mg, -5.5 (-6.5, -4.4)/-3.0 (-3.7, -2.3) mm Hg; aliskiren 300 mg, -8.7 (-9.7, -7.6)/-5.0 (-5.6, -4.3) mm Hg (Musini et al., 2009).

Several clinical trials revealed that aliskiren/HCTZ combination therapy reduced SBP and DBP from baseline to a significantly greater extent than placebo, aliskiren monotherapy and HCTZ monotherapy (Chrysant 2008; Baldwin and Plosker 2009). Aliskiren/HCTZ also produced significant additional SBP and DBP reductions in patients inadequately responsive to 4 weeks' prior treatment with aliskiren or HCTZ alone (Baldwin and Plosker 2009). Single-pill combinations (SPCs) of aliskiren/HCTZ (150/12.5 mg, 150/25 mg, 300/12.5 mg, 300/25 mg) have recently been approved by the US FDA (18th January 2008) and by EMEA (16th January 2009) for the treatment of adults with essential hypertension whose BP is not adequately controlled with aliskiren or HCTZ alone, and as a substitution treatment in patients with hypertension adequately treated by the two individual drugs concomitantly at the equivalent fixed dosage. In this chapter, we briefly reviewed the pharmacodynamic and pharmacokinetic profile of aliskiren and assessed the antihypertensive efficacy and tolerability of the aliskiren/HCTZ combination therapy in reducing SBP and DBP in patients with mild to moderate hypertension by using a systematic review of the literature and a meta-analytical approach to combine data from different clinical trials.

2. Aliskiren: Pharmacodynamic and pharmacokinetic properties

A schematic of the RAAS is depicted in Figure 1. Renin is an aspartic protease produced by the juxtaglomerular cells in the kidney. This enzyme catalyses the cleavage of angiotensinogen, the only know substrate of renin, to the decapeptide angiotensin I (Ang I). This is the rate-limiting step of RAAS activation. In the presence of ACE, Ang I is converted into the octapeptide hormone Ang II, a potent vasoconstrictor that mediates its activity through the type-1 angiotensin II (AT1) receptor. Binding of Ang II to AT1 receptor increases BP, and promotes aldosterone secretion from adrenal cortex, sodium reabsorption in renal proximal tubules, and catecholamine release from pre-synaptic nerve endings and adrenal medulla (Kim and Iwao 2000). Pathological activation of RAAS can result in high BP with consequent end-organ damage.

Several drugs can inhibit the RAAS cascade but redundant biochemical pathways limit the potential beneficial effects of these drugs.

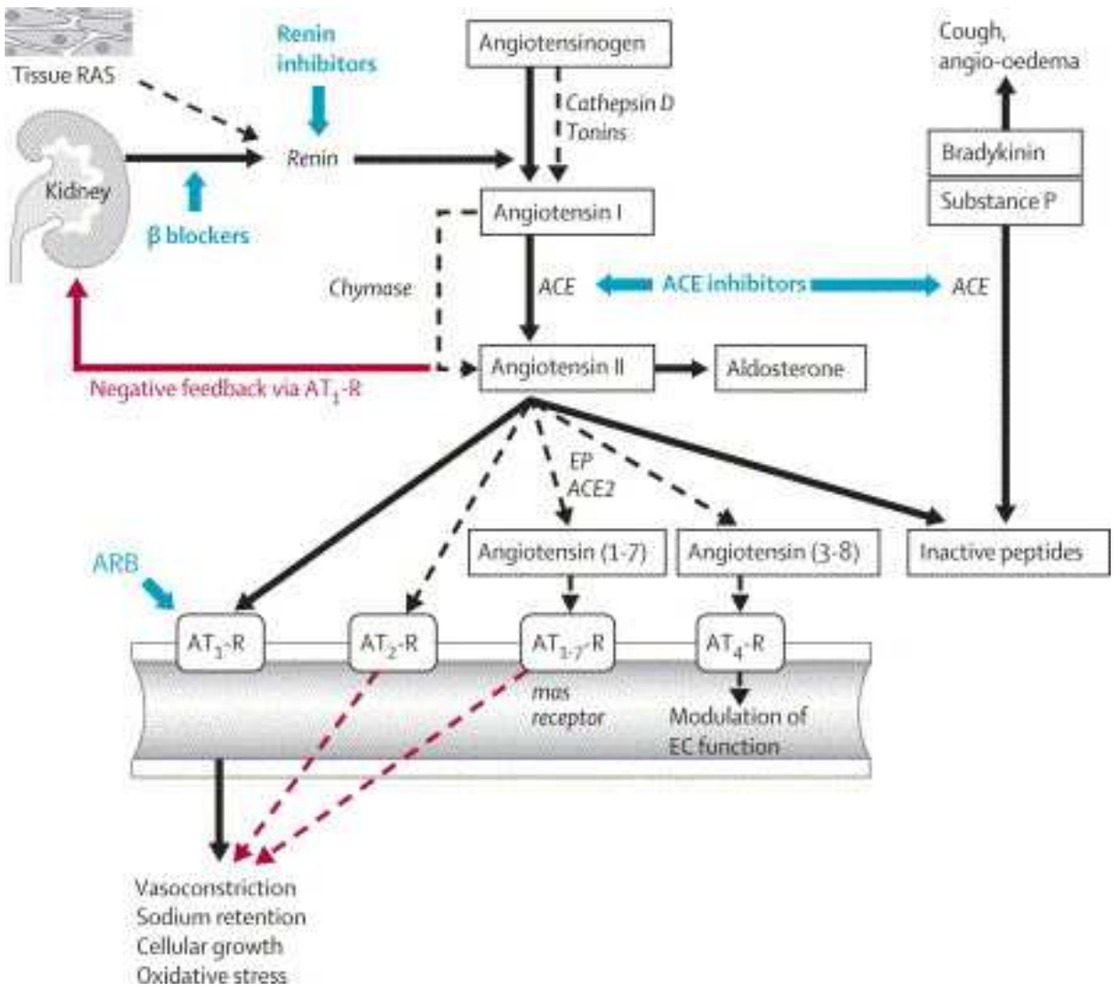

Fig. 1. The renin-angiotensin-aldosterone system (Staessen et al., 2006). Black arrows show stimulation and red arrows show inhibition. Dotted lines show alternative pathways mainly documented in experimental studies. Beta-blockers, renin inhibitors, inhibitors of angiotensin-converting enzyme (ACE) and angiotensin II type-1 receptor blockers (ARB) reduce the activity of the renin-angiotensin system (RAS). Abbreviations: AT-R, angiotensin receptor; EP, endopeptidases; EC, endothelial cells. From reference Staessen et al., with permission from Elsevier.

ACE inhibitors block the conversion of Ang I to Ang II but non-ACE pathways of Ang II generation such as a chymase and presumably other enzymes pathways present in end organs including heart, kidney and blood vessels get activated under conditions of ACE inhibition (Urata et al., 1996; Hollenberg et al., 1998). The existence of alternative pathways for Ang II generation that are unaffected by ACE inhibitors raises questions about whether ACE is the optimal target for RAAS suppression. Furthermore, ACE inhibitors are not specific for RAAS and can prevent ACE-induced inactivation of bradykinin and substance P that are thought to be responsible for ACE-inhibitor related side effects as cough and angioedema. ARBs exert their effect by blocking AT1 receptors activation by Ang II. This may lead to unbalanced activation of other types of receptors such as type-2 and type-4 Ang

II receptors (AT2 and AT4 receptors). Physiological role of these receptors are not clear but may be important for endothelial function (Wantanabe et al 2005). Over stimulation of AT2 receptors can generate deleterious agents such as oxygen free radicals, pro-inflammatory cytokines and pro-fibrotic mediators and may promote left ventricular hypertrophy (Williams 2001; Azizi et al 2006). On the other hand, beneficial effects such as inhibition of renin synthesis and Ang II formation are also reported following AT2 receptor activation (Siragy et al 2005). Both ACE inhibitors and ARBs stimulate renal renin production by interrupting the normal feedback suppression of renin secretion from the kidneys. The reactive rise in circulating active renin leads to greater generation of Ang II via pathways dependent or independent of ACE.

2.1 Pharmacodynamic properties of aliskiren

Recently, a new blocker of RAAS, aliskiren, has been developed and approved for the treatment of hypertension. Aliskiren is a direct inhibitor of renin, the enzyme that catalyses the conversion of angiotensinogen to Ang I. This is the rate limiting step in the production of the end product of RAAS cascade, which makes renin inhibition an attractive option for effective RAAS blockade. Renin is measured as plasma renin concentration (PRC) and plasma renin activity (PRA). PRC measures the actual amount of renin in plasma regardless of its enzymatic activity and is expressed as either μU/mL or pg/mL. PRA denotes the enzymatic activity of renin and is measured as the rate of Ang I production after adding serum to angiotensinogen and is expressed as ng/ml/hour. Like ACE inhibitors and ARBs, aliskiren can reactively lead to an increase in PRC. However, unlike these other inhibitors of the RAAS, the effects of renin are suppressed with aliskiren, resulting in a reduction in PRA.

Aliskiren is a small molecular weight, orally active, non-peptide direct renin inhibitor with very high affinity and specificity for human and primate renin (Wood et al., 2003). It is significantly less active against renin from dogs, rats, rabbits, pigs and cats, which made the process of conducting preclinical experimental studies a challenging one (Wood et al., 2003). As a result, these preclinical studies have been performed in marmosets (primates) and double-transgenic rats that express the human renin and human angiotensinogen genes (Pilz et al., 2005; Wood et al., 2005).

Aliskiren is a potent inhibitor of renin with an IC_{50} (concentration inhibiting 50% of activity) of 0.6 nmol/L. Aliskiren oral doses of 3 and 10 mg/kg completely suppressed PRA for 24 hours in mildly sodium depleted marmosets (Wood et al., 2005; Vaidyanathan et al., 2006; O'Brien et al., 2007; Vaidyanathan et al., 2007a; Vaidyanathan et al., 2007b). It decreased PRA, Ang I and Ang II levels in normotensive volunteers in a dose dependent manner but caused a 10-fold increase in PRC (Nussberger et al., 2002). A decrease in plasma and urine aldosterone levels were also noted with daily aliskiren doses of 80 mg and above (Nussberger et al., 2002).

Effects of various medications on RAAS pathway are shown in Table 1. With the exception of beta-blockers, all other agents blocking RAAS and diuretics including HCTZ increase PRC. Aliskiren and ACE inhibitors achieve this by decreasing Ang II levels and ARBs by blocking inhibitory effects of Ang II on AT1 receptors on juxtaglomerular cells. Diuretics increase PRC by inducing volume depletion. The extent of PRC elevation is more marked when aliskiren is combined with HCTZ. PRA is increased by ACE inhibitors, ARBs and

HCTZ while aliskiren use alone and in combination with HCTZ is associated with a decrease in PRA. Other agents that can decrease PRA include beta-blockers and central alfa-2 receptor agonists.

Antihypertensive medications	Enzymes		Substrates	End-products			
	PRC	PRA	Angiotensinogen	Ang I	Ang II	Ang_{1-7}	Aldosterone
Beta-blockers	↓	↓	–	↓	↓	↓	↓
ACE inhibitors	↑	↑	↓	↑	↓	↑	↓
ARBs	↑	↑	↓	↑	↑	↑	↓
Aliskiren	↑↑	↓↓	-	↓	↓	↓	↓
HCTZ	↑	↑	↓	↑	↑	↑	↑
Aliskiren/HCTZ combination	↑↑↑	↓	–	–	–	–	–

Abbreviations: ACE, angiotensin-converting enzyme; Ang I, angiotensin I; Ang II, angiotensin II; Ang 1–7, angiotensin 1–7; ARBs, angiotensin II type-1 receptor blockers; HCTZ, hydrochlorothiazide; PRA, plasma renin activity; PRC, plasma renin concentration; ↑, increased; ↓, decreased; −, unchanged or unknown. Adapted from (Sureshkumar 2008).

Table 1. Antihypertensive medication effects on RAAS pathway

2.2 Pharmacokinetic properties of aliskiren

The pharmacokinetic properties of aliskiren have been studied in animals, healthy human subjects, patients with compromised liver and kidney function, and subjects with mild hypertension (Waldmeier et al., 2007). Aliskiren has a poor bioavailability (2-6%), but this is compensated by its high solubility and the already mentioned high inhibitory effect (IC_{50} = 0.6 nM) from *in vitro* inhibition of human renin (Wood et al., 2005; Azizi et al., 2006).

After oral administration, peak plasma concentrations (Cmax) of aliskiren are reached within 1–3 hours (Vaidyanathan et al., 2006; Zhao et al., 2006). When taken with a high-fat meal, the mean area under the plasma concentration–time curve (AUC) and Cmax of aliskiren are decreased by 71% and 85%, respectively (Novartis_Europharm_Limited 2007. Available at http://www.ema.europa.eu/docs/pt_PT/document_library/EPAR_-_Product_Information/human/000780/WC500047010.pdf. Accessed on 27th August 2011). Steady state is achieved after approximately 7 days with once daily dosing (Nussberger et al., 2002). Aliskiren is not extensively bound (49.5%) to plasma proteins (Novartis Europharm Limited, 2007). The volume of distribution at steady state is 135 L (Novartis Europharm Limited, 2007).

Aliskiren undergoes minimal hepatic metabolism. *In vitro* studies indicate that aliskiren is a substrate of the cytochrome P450 (CYP) 3A4 isoenzyme; however, it is neither an inhibitor nor an inducer of CYP isoenzymes (Vaidyanathan et al., 2006). Aliskiren is primarily eliminated by the hepatobiliary route as unmetabolized drug. Less than 1% of an orally administered dose is excreted in the urine as unchanged drug (Waldmeier et al., 2007). After oral administration of a single 300-mg dose of aliskiren to healthy volunteers, the mean ± SD clearance corrected for bioavailability [i.e., clearance/drug bioavailability (Cl/F)] was 234 ± 137 L/hour (Zhao et al., 2006). The terminal half-life of aliskiren ranges from 24–40 hours (Nussberger et al., 2002; Azizi et al., 2004; Zhao et al., 2006). This half-life, which is longer than the 24-hour dosing interval, is consistent with the observation that plasma

concentrations of aliskiren have been shown to accumulate by about 2-fold at steady state compared with administration of a single dose (Vaidyanathan et al., 2006).

3. Aim of the review

The aim of this review was to assess the antihypertensive efficacy and tolerability of the aliskiren/HCTZ combination therapy (as a combination of the individual components or as SPCs) in reducing SBP and DBP in patients with mild to moderate hypertension by using systematic analysis of the literature and meta-analytical approach to combine data from different randomized, double-blind, clinical trials.

4. Methodology for selection of clinical trials and data analysis

A literature search to identify clinical trials using aliskiren in combination with HCTZ for the treatment of hypertension was conducted on July 2011 to obtain all published study reports that met our inclusion criteria.

4.1 Inclusion and exclusion criteria

We included all articles in the literature written in any of the major languages. To be included in our review studies were required to be randomized, double-blind, clinical trials using aliskiren in combination with HCTZ (as a combination of the individual components or as SPCs) for the treatment of hypertension. Additionally, studies were included if they evaluated the antihypertensive efficacy [outcome measure) of aliskiren/HCTZ in patients with mild or moderate essential hypertension (SBP 140-179 mm Hg and/or DBP 90-109 mm Hg, as defined in current international guidelines (Mancia et al., 2007)] and patient age ≥ 18 years. Articles were automatically excluded if their results were not reported or had been presented in forms such as abstracts, letters, or commentaries.

4.2 Literature search strategy

We searched the following electronic databases: International Pharmaceutical Abstracts, MEDLINE, The Cochrane Library and ISI Web of Knowledge. Each database was independently searched by 2 reviewers for articles published from 2000 to and including June 30, 2011, using the search terms *aliskiren*, *aliskiren/hydrochlorothiazide*, *aliskiren-hydrochlorothiazide*, *aliskiren in combination with hydrochlorothiazide*, *renin inhibitor*. The reviewers selected articles based on the predefined inclusion/exclusion criteria and results were matched. A consensus method was applied to judge any article selection divergences. The rationale for decisions was discussed until reviewers agreed on the final decision. A third author was called to resolve any remaining discrepancies concerning article eligibility.

Selected articles' references and reviews of the subject were hand searched for additional studies that were not obtained through our initial electronic search.

4.3 Data extraction

The following information was gathered for each clinical trial: author names, year of publication, study design and duration, setting, characteristics of the patients enrolled, sizes

of the treatment groups, daily treatment regimens and primary endpoint. Outcomes extracted from articles included mean and variation of SBP and DBP at baseline and final assessments for each group, responder rate (DBP < 90 mm Hg or ≥10 mm Hg reduction from baseline) and BP control rate (SBP < 140 mm Hg and DBP < 90 mm Hg). Changes from baseline in PRA and PRC with aliskiren/HCTZ and with either component alone were also extracted whenever reported, as well as adverse events recorded during the trials. During the data extraction phase, we wrote to corresponding authors of studies to request missing data and clarify study details.

4.4 Quality assessment

The quality of selected articles was assessed by the same principles used in article selection and data extraction (i.e., 2 independent reviewers), and was based on the Jadad et al. method to measure the risk of bias (Jadad et al., 1996). Their 3-item quality assessment checklist evaluates the following methodological parameters: controlled trial, random allocation of treatments, double-blind follow-up, dropout rate, intention-to-treat (ITT) analysis and absence of other biases. Quality scores were presented as proportions of the total possible score (i.e., 5) of the quality assessment scale (where 100% represents the maximum quality). The scores were categorized according to the following criteria: weak (<60%), fair (60%), good (80%), or very good (100%).

4.5 Analysis method

For trials meeting the criteria for inclusion in the analysis, the efficacy of treatment was evaluated via measurements of SBP and DBP at the start of the trial (baseline) and after 8 weeks of therapy. The meta-analytical approach therefore compared the efficacy of each aliskiren/HCTZ dose combination in reducing SBP and DBP over this period of time. The analysis method used was based on calculation of the mean BP reduction for a set of aliskiren/HCTZ dose combinations evaluated, by weighting the combined data for the trial size using the following formula: (BP reduction [trial 1] • number of patients [trial 1] +…+ BP reduction [trial n] • number of patients [trial n])/total number of patients (trial 1 +…+ trial n).

5. Results

A completed QUOROM flow chart (Moher et al., 1999) of the literature search strategy applied and results found is depicted in Figure 2. Initially, 52 potentially relevant RCTs were identified that appeared to meet the inclusion criteria and were screened for retrieval based on their titles and abstracts. Thirty-six of those articles were excluded for not evaluating aliskiren in combination with hydrochlorothiazide. The remaining 16 articles were retrieved for full-text review. Eleven of those articles were excluded for the following reasons: two had data that were not extractable (Andersen et al., 2008; Andersen et al., 2009), three presented excluded study designs (O'Brien et al., 2007; Chrysant et al., 2008; Littlejohn et al., 2009), one enrolled patients with severe hypertension (Strasser et al., 2007), four appeared only in the abstract form (Sica et al., 2006; Gradman et al., 2007; Prescott et al., 2007; Calhoun et al., 2008) and one was indexed in MEDLINE in duplicate (Nickenig et al., 2008). Therefore, after exclusion criteria were applied, a total of 5 studies involving a total of 5508 patients were included in this analysis [20-24].

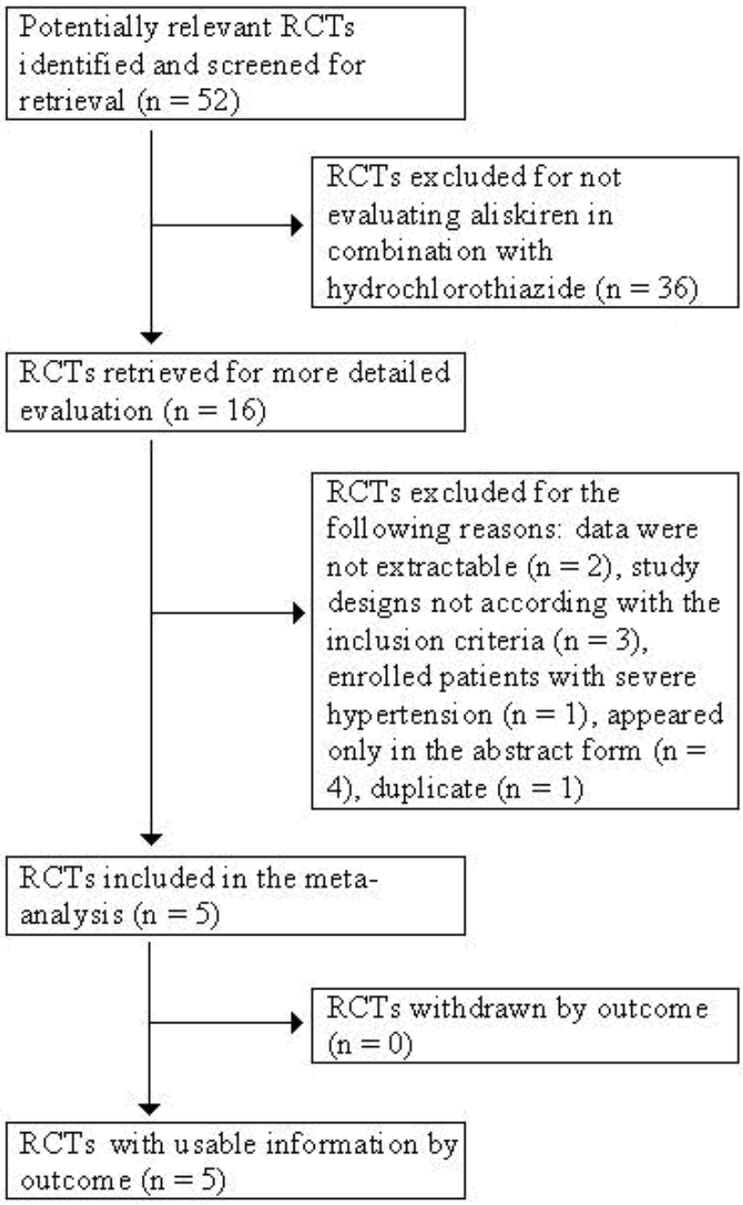

Fig. 2. Quorom flow chart of literature search strategy applied and results. Five double-blind randomized controlled trials met the inclusion criteria, using aliskiren in combination with HCTZ for the treatment of hypertension.

Table 2 presents the overall characteristics of the evaluated studies. The average sample size was 1102 ± 947 (mean ± SD), with a median of 722 and range from 489–2776 patients. All included studies were randomized, double-blind, multicenter clinical trials, proceeded by a single-blind, placebo (Villamil et al., 2007) / active comparator (Jordan et al., 2007; Nickenig et al., 2008; Blumenstein et al., 2009; Geiger et al., 2009), run-in period of 2-4 weeks. Moreover, all five studies specified the change from baseline (start of double-blind treatment) in mean sitting DBP (msDBP) at 8 weeks as the primary endpoint.

Reference (Year)	Study Design, Duration, Setting, BP measurement, No of patients	Demographics and Baseline Characteristics[a]	Daily Treatment Regimens	Primary End Point	Quality Score[b]
Villamil (2007)	Randomized, double-blind, placebo-controlled, multicenter; 8 wks; clinic; trough BP; n=2776	Age ≥ 18 yrs. Eligibility for single-blind phase: msDBP ≥95 and <110 mmHg (baseline). Eligibility for double-blind phase: msDBP ≥95 and <110 mmHg after 2 or 4 wks on placebo. Mean age 55 yrs; 55% men; 86% Caucasian.	Single-blind, placebo run-in period (2 wks or 4 wks): Placebo. Double-blind treatment (8 wks): Placebo; Aliskiren 75, 150, 300mg; HCTZ 6.25, 12.5, 25mg; Aliskiren/HCTZ 75/6.25, 75/12.5, 75/25, 150/6.25, 150/12.5, 150/25, 300/12.5, 300/25mg.	Change in msDBP from baseline (start of double-blind treatment) to wk 8 endpoint (aliskiren monotherapy vs placebo; combination therapy vs respective monotherapies)	60%[c]
Jordan (2007)	Randomized, double-blind, multicenter; 12 wks; clinic; trough BP; n=489	Age ≥ 18 yrs. Eligibility for single-blind phase: msDBP ≥95 and <110 mmHg (baseline). Eligibility for double-blind phase: msDBP ≥90 and <110 mmHg. BMI ≥ 30 kg/m^2; Mean age 54 yrs; 44% men; 99.6% Caucasian.	Single-blind treatment (4 wks): HCTZ 25mg. Double-blind treatment (first 4 wks – next 8 wks): Placebo–HCTZ 25 – 25mg; Aliskiren/HCTZ 150/25 - 300/25mg; Irbesartan/HCTZ 150/25 – 300/25 mg; Amlodipine/HCTZ 5/25 – 10/25mg.	Change in msDBP from baseline (start of double-blind treatment) to wk 8 endpoint (aliskiren/HCTZ 300/25 mg vs placebo–HCTZ 25 mg)	100%
Nickenig (2008)	Randomized, double-blind, multicenter; 8 wks; clinic; trough BP; n=880	Age ≥ 18 yrs. Eligibility for single-blind phase: msDBP ≥95 and <110 mmHg or msDBP ≥85 and <110 mmHg if treated for HT within the 4 wks prior to screening (baseline). Eligibility for double-blind phase: msDBP ≥90 and <110 mmHg after 4 wks of aliskiren 300 mg monotherapy. Mean age 55 yrs;55% men;83% Caucasian.	Single-blind treatment (4 wks): Aliskiren 300mg. Double-blind treatment (8 wks): Aliskiren 300mg; Aliskiren/HCTZ 300/12.5, 300/25mg.	Change in msDBP from baseline (start of double-blind treatment) to wk 8 endpoint (aliskiren monotherapy vs combination therapy)	100%
Blumenstein (2009)	Randomized, double-blind, multicenter; 8 wks; clinic; trough BP; n=722	Age ≥ 18 yrs. Eligibility for single-blind phase: patients with HT, who were newly diagnosed, untreated or treated at the time of screening. Newly diagnosed pts or pts who had not been treated for HT in the 4 wks prior to screening had to have msDBP ≥95 and <110 mmHg at the time of the screening. Eligibility for double-blind phase: msDBP ≥90 and <110 mmHg after 4 wks of HCTZ 25 mg monotherapy. Mean age 54 yrs; 59% men;91% Caucasian.	Single-blind treatment (4 wks): HCTZ 25mg. Double-blind treatment (8 wks): HCTZ 25mg; Aliskiren/HCTZ 150/25, 300/25mg.	Change in msDBP from baseline (start of double-blind treatment) to wk 8 endpoint (HCTZ monotherapy vs combination therapy)	100%

Reference (Year)	Study Design, Duration, Setting, BP measurement, No of patients	Demographics and Baseline Characteristics[a]	Daily Treatment Regimens	Primary End Point	Quality Score[b]
Geiger (2009)	Randomized, double-blind, multicenter; 8 wks; clinic; trough BP; n=641	Age ≥ 18 yrs. Eligibility for single-blind phase: pts with mild to moderate HT taking antihypertensive agents. Eligibility for double-blind phase: msDBP ≥95 and <110 mmHg after 4 wks of HCTZ monotherapy. Mean age 53 yrs; 57% men; 86% Caucasian.	Single-blind treatment (4 wks): HCTZ 12.5mg for 1 wk followed by HCTZ 25mg for 3 wks. Double-blind treatment (8 wks): HCTZ 25mg; Aliskiren/HCTZ 150/25mg for 4 wks followed by 300/25mg for another 4 wks; Valsartan/HCTZ 160/25mg for 4 wks followed by 320/25mg for another 4 wks; Aliskiren/Valsartan/HCTZ 150/160/25mg for 4 wks followed by 300/320/25mg for another 4 wks.	Change in msDBP from baseline (start of double-blind treatment) to wk 8 endpoint (aliskiren/HCTZ and valsartan/HCTZ vs aliskiren/valsartan/ HCTZ)	60%[d]

[a]In each published clinical trial, patient baseline and demographic characteristics were comparable for all treatment groups.
[b]The percentage of the total possible score (i.e., 5) of the quality assessment scale applied (100% represents the maximum quality).
[c]Method to generate the sequence of randomization and method of double blind were not described; additionally, some information on outcome variability was not provided.
[d]Method to generate the sequence of randomization and method of double blind were not described.
Abbreviations: BP, blood pressure; HCTZ, hydrochlorothiazide; HT, hypertension; msDBP, mean sitting diastolic blood pressure; pts, patients; wk, week.

Table 2. Published clinical trials of aliskiren/HCTZ for treatment of mild to moderate hypertension

Secondary efficacy measures included the change in mean sitting SBP (msSBP) (Jordan et al., 2007; Villamil et al., 2007; Nickenig et al., 2008; Blumenstein et al., 2009; Geiger et al., 2009), the proportion of patients with successful response to treatment (defined as msDBP < 90 mmHg and/or a ≥ 10 mmHg reduction from baseline) (Jordan et al., 2007; Villamil et al., 2007) and the proportion of patients attaining BP control (defined as msDBP < 90 mmHg and msSBP < 140 mm Hg) (Jordan et al., 2007; Villamil et al., 2007; Nickenig et al., 2008; Blumenstein et al., 2009; Geiger et al., 2009). Two trials used the SPC (Jordan et al., 2007; Villamil et al., 2007), and three combined the individual components (Nickenig et al., 2008; Blumenstein et al., 2009; Geiger et al., 2009), with aliskiren and HCTZ administered orally as single daily doses in all studies. One trial enrolled obese hypertensive patients only (obesity defined as body mass index of ≥ 30 kg/m^2) (Jordan et al., 2007), although in the remaining four trials subgroups of patients with obesity were also present. In the five included clinical trials patient demographics and baseline characteristics were similar across treatment groups. Brief details of the characteristics of each individual trial and treatment group, including mean patient ages, sex ratios, body mass index / obesity and baseline SBP and DBP are provided in Table 3.

Reference	Pts., n	Treatment and daily dose (mg)	Patient age (years)	Sex ratio (M/F)	BMI (kg/m²)	Obese (BMI ≥ 30 kg/ m²) (%)	SBP baseline (mm Hg)	DBP baseline (mm Hg)
Villamil (2007)	195	Placebo	54.4	109/86	NR	40.5	152.7	99.3
	184	Aliskiren 75	55.0	103/81	NR	41.8	153.2	99.4
	185	Aliskiren 150	53.5	112/73	NR	32.4	153.4	98.8
	183	Aliskiren 300	54.2	99/84	NR	38.8	154.4	99.3
	194	HCTZ 6.25	55.2	109/85	NR	41.2	153.4	99.3
	188	HCTZ 12.5	55.4	103/85	NR	38.8	153.4	99.1
	176	HCTZ 25	55.1	92/84	NR	32.4	154.5	99.1
	188	Aliskiren/HCTZ 75/6.25	55.1	108/80	NR	37.8	154.5	98.9
	193	Aliskiren/HCTZ 75/12.5	54.4	101/92	NR	39.9	154.0	100.0
	186	Aliskiren/HCTZ 75/25	54.7	101/85	NR	38.7	152.9	99.0
	176	Aliskiren/HCTZ 150/6.25	53.9	96/80	NR	37.5	153.3	99.0
	186	Aliskiren/HCTZ 150/12.5	54.7	98/88	NR	35.5	154.1	99.1
	188	Aliskiren/HCTZ 150/25	53.7	104/84	NR	37.8	153.2	98.4
	181	Aliskiren/HCTZ 300/12.5	55.5	89/92	NR	42.0	153.2	99.5
	173	Aliskiren/HCTZ 300/25	54.8	98/75	NR	41.0	154.6	99.3
Jordan (2007)	122	HCTZ 25	55.2±12.3	52/70	34.0±4.1	NR	149.5±11.3	97.2±4.6
	122	Aliskiren/HCTZ 300/25	53.1±11.9	60/62	34.8±5.2	NR	149.4±11.6	96.8±4.9
	119	Irbesartan/HCTZ 300/25	53.0±11.0	48/71	34.3±4.7	NR	149.1±13.4	96.6±4.4
	126	Amlodipine/HCTZ 10/25	55.2±11.9	53/73	34.5±4.1	NR	149.8±11.5	96.7±5.0
Nickenig (2008)	298	Aliskiren 300	55.5±10.6	159/139	29.2±4.5	NR	149.8±12.6	95.5±4.4
	293	Aliskiren/HCTZ 300/12.5	54.9±10.5	155/138	29.2±4.9	NR	150.3±12.5	95.5±4.3
	289	Aliskiren/HCTZ 300/25	54.4±10.3	172/117	28.9±4.6	NR	150.8±12.8	95.8±4.7
Blumenstein (2009)	246	HCTZ 25 mg	52.9±11.5	143/103	29.7±5.0	NR	151.8±11.9	96.3±4.9
	244	Aliskiren/HCTZ 150/25	53.6±11.1	144/100	28.9±4.7	NR	151.2±12.7	96.1±4.9
	232	Aliskiren/HCTZ 300/25	54.1±9.5	140/92	29.9±5.0	NR	151.1±12.3	96.1±4.6
Geiger (2009)	152	HCTZ 25	52.6±9.93	94/58	31.8±6.13	NR	154.1±12.61	99.9±4.33
	166	Aliskiren/HCTZ 300/25	52.3±10.90	92/74	31.3±6.28	NR	153.3±12.68	99.3±4.10
	155	Valsartan/HCTZ 320/25	55.0±11.40	88/67	31.3±5.85	NR	156.7±12.49	99.9±3.97
	168	Aliskiren/Valsartan/HCTZ 300/320/25	52.9±10.83	91/77	31.9±6.21	NR	152.7±11.64	99.2±3.70

Values are mean ±SD unless otherwise stated.
Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; F, female; HCTZ, hydrochlorothiazide; M, male; NR, not reported; Pts, patients; SBP, systolic blood pressure.

Table 3. Main patient baseline and demographic characteristics by treatment group of the included clinical trials (randomized population)

The average quality score of study reporting was 84% ± 22% (range 60–100%), which could be categorized as very good. One study failed to report all information on data variability (Villamil et al., 2007), which prevented the use of an approximation for standard error of the mean (SEM) or confidence interval (CI) estimation, when calculating some weighted average reductions in SBP and DBP. We contacted the corresponding author of this study by email to request missing data on SEM as well as on BP control rate at endpoint for each aliskiren/HCTZ, aliskiren and HCTZ daily doses tested, but no response was provided.

Table 4 details results from clinical trials on the efficacy of aliskiren/HCTZ in reducing BP. In the only placebo-controlled study (and also the largest of the RCTs), aliskiren/HCTZ combination reduced SBP and DBP from baseline to a significantly ($p \leq 0.0001$) greater extent than placebo in patients with mild to moderate hypertension (Villamil et al., 2007).

Reference	Patients, n (ITT)	Treatment and daily dose (mg)	Change in SBP from baseline at endpoint (mm Hg)	Change in DBP from baseline at endpoint (mm Hg)	Responder rate (%)	BP control rate at endpoint (%)
Villamil (2007)	192	Placebo	-7.5	-6.9	45.8	28.1
	183	Aliskiren 75	-9.4	-8.7±0.59[a]	51.9	(29.0
	183	Aliskiren 150	-12.2[b]	-8.9±0.59[a]	51.9	to
	180	Aliskiren 300	-15.7[c]	-10.3±0.60[c]	63.9[b]	[c] 46.7)
	194	HCTZ 6.25	-11.0[a]	-9.1±0.58[a]	53.6	(32.5
	188	HCTZ 12.5	-13.9[c]	-10.1±0.59[c]	60.6[a]	to
	173	HCTZ 25	-14.3[c]	-9.4±0.61[a]	59.0[a]	37.8)
	187	Aliskiren/HCTZ 75/6.25	-14.3 ±0.93[c,d]	-10.8[c,d]	61.5[a]	
	189	Aliskiren/HCTZ 75/12.5	-15.6[c]	-11.1[c]	63.5[b]	[a]
	186	Aliskiren/HCTZ 75/25	-17.3[c,d]	-11.5[c,d]	70.4[c,d]	[a,d]
	173	Aliskiren/HCTZ 150/6.25	-15.3[c]	-10.4±0.59[c]	58.4[a]	[a] (37.4
	184	Aliskiren/HCTZ 150/12.5	-17.6[c,d]	-11.9[c,d]	69.6[c]	[a,d] to
	187	Aliskiren/HCTZ 150/25	-19.5[c,d]	-12.7[c,d]	71.1[c,d]	[a,d] 59.5)
	180	Aliskiren/HCTZ 300/12.5	-19.8[c,d]	-13.9[c,d]	80.6[c,d]	[a,d]
	173	Aliskiren/HCTZ 300/25	-21.2±0.97[c,d]	-14.3±0.61[c,d]	76.9[c,d]	[a,d]
Jordan (2007)	117	HCTZ 25	-8.6±1.00	-7.9±0.73	59.0	34.2
	113	Aliskiren/HCTZ 300/25	-15.8±1.01[e]	-11.9±0.74[e]	73.5[f]	56.6[g]
	117	Irbesartan/HCTZ 300/25	-15.4±1.00[h]	-11.3±0.72[h]	70.9[h]	54.7[h]
	122	Amlodipine/HCTZ 10/25	-13.6±0.98[h]	-10.3±0.71[h]	68.0[h]	45.1[i]
Nickenig (2008)	296	Aliskiren 300	-8.0±0.9	-7.4±0.5	62.2	40.9
	292	Aliskiren/HCTZ 300/12.5	-13.5±0.9[j]	-10.5±0.5[j]	73.3[k]	57.9[j]
	284	Aliskiren/HCTZ 300/25	-15.9±0.9[j]	-11.0±0.6[j]	77.1[j]	60.2[j]
Blumenstein (2009)	244	HCTZ 25 mg	-7.1±0.7	-4.8±0.4	47.1	25.8
	242	Aliskiren/HCTZ 150/25	-12.9±0.7[l]	-8.5±0.4[l]	67.4[l]	48.8[l]
	232	Aliskiren/HCTZ 300/25	-16.7±0.7[l,m]	-10.7±0.4[l,n]	78.5[l]	58.2[l,o]
Geiger (2009)	151	HCTZ 25	-6±1.12	-6±0.70	NR	20.53
	164	Aliskiren/HCTZ 300/25	-15 ±1.08[l]	-11±0.67[l]	NR	40.85[l]
	154	Valsartan/HCTZ 320/25	-18 ±1.12[l]	-14±0.70[l]	NR	48.70[l]
	168	Aliskiren/Valsartan/HCTZ 300/320/25	-22±1.07[l,p,q]	-16±0.67[l,p,q]	NR	66.67[l,p,r]

Changes in blood pressure are presented as the least-squares mean changes (with ± SEM, whenever provided by the authors).
[a]P < 0.05, [b]P < 0.001, [c]P ≤ 0.0001 vs placebo; [d]P < 0.05 vs each component monotherapy; [e]P < 0.0001 vs HCTZ 25 mg; [f]P < 0.05 vs HCTZ 25 mg; [g]P = 0.0005 vs HCTZ 25 mg; [h]P > 0.05 vs aliskiren/HCTZ 300/25 mg; [i]P = 0.052 vs aliskiren/HCTZ 300/25 mg; [j]P < 0.001 vs aliskiren 300 mg; [k]P = 0.002 vs aliskiren 300 mg; [l]P < 0.001 vs HCTZ 25 mg; [m]P = 0.009 vs aliskiren/HCTZ 150/25 mg; [n]P < 0.001 vs aliskiren/HCTZ 150/25 mg; [o]P = 0.033 vs aliskiren/HCTZ 150/25 mg; [p]P < 0.001 vs aliskiren/HCTZ 300/25 mg; [q]P < 0.01 vs valsartan/HCTZ 320/25 mg; [r]P < 0.001 vs valsartan/HCTZ 320/25 mg.
Abbreviations: BP, blood pressure; DBP, diastolic blood pressure; HCTZ, hydrochlorothiazide; ITT, intention-to-treat analysis; NR, not reported; SBP, systolic blood pressure.

Table 4. Clinical trial data on the efficacy of aliskiren/HCTZ in reducing blood pressure

Furthermore, aliskiren/HCTZ combination (at all but the 75/12.5 mg and 150/6.25 mg dosages, both of which are not commercially available) decreased SBP and DBP from baseline to a significantly ($p < 0.05$) greater extent than the component monotherapies (Villamil et al., 2007). In the other selected RCTs, all of which with an active comparator and a non-responder study design (Jordan et al., 2007; Nickenig et al., 2008; Blumenstein et al., 2009; Geiger et al., 2009), aliskiren/HCTZ combination was an effective treatment option, producing significantly additional reductions in SBP and DBP in patients with mild to moderate hypertension inadequately responsive to 4 weeks' prior treatment with aliskiren

(Nickenig et al., 2008) or HCTZ (Jordan et al., 2007; Blumenstein et al., 2009; Geiger et al., 2009) alone. In the five included RCTs, BP control rates were also significantly higher with all aliskiren/HCTZ combinations commercially available than with placebo, aliskiren alone and HCTZ alone. One of the included studies did not report the BP response rate (Geiger et al., 2009), in the remaining four studies, BP response rates were also significantly higher with all aliskiren/HCTZ combinations commercially available than with placebo; however, only the three higher dosages of aliskiren/HCTZ combinations yielded significantly higher BP response rates than the component monotherapies (Jordan et al., 2007; Villamil et al., 2007; Nickenig et al., 2008; Blumenstein et al., 2009).

Two studies also compared the efficacy of aliskiren/HCTZ 300/25 mg combination in reducing and controlling BP with other treatment combinations (amlodipine/HCTZ 10/25 mg, irbesartan/HCTZ 300/25 mg, valsartan/HCTZ 320/25 mg and aliskiren/valsartan/HCTZ 300/320/25 mg) (Jordan et al., 2007; Geiger et al., 2009). Only the last combination yielded significantly greater decreases in SBP and DBP and higher BP control rates than the aliskiren/HCTZ 300/25 mg combination (Geiger et al., 2009).

Aliskiren/HCTZ combination evaluated	Number of clinical trials	Total number of patients	Change in SBP from baseline at endpoint (mm Hg)	Change in DBP from baseline at endpoint (mm Hg)	BP control rate (%)[a]
Aliskiren/HCTZ 150/12.5 mg	1	184	-17.6	-11.9	[37.4, 59.5][a]
Aliskiren/HCTZ 150/25 mg	2	429	-15.8	-10.3	[43.8, 53.5][a]
Aliskiren/HCTZ 300/12.5 mg	2	472	-15.9	-11.8	[50.1, 58.5][a]
Aliskiren/HCTZ 300/25 mg	5	966	-16.9±0.4	-11.6±0.3	[51.9, 55.9][a]

Changes in blood pressure are presented as the weighted least-squares mean changes ± SEM (not all variability information was provided in the trial of Villamil (2007), preventing the use of an approximation for SEM or confidence intervals estimation for the first three aliskiren/HCTZ dose combinations).
[a]The range presented is due to the trial of Villamil (2007), which presented the range of BP control rate for aliskiren/HCTZ combination, without specify the values for each dose combination.
Abbreviations: BP, blood pressure; DBP, diastolic blood pressure; HCTZ, hydrochlorothiazide; SBP, systolic blood pressure.

Table 5. Weighted average reductions from baseline of SBP and DBP and BP control rate for each aliskiren/HCTZ combination commercially available

The Q statistic for heterogeneity of effects was not significant, both for SBP ($\chi^2 = 1.14$, $p = 0.89$) and for DBP ($\chi^2 = 0.62$, $p = 0.96$); therefore we considered the study results to be combinable and a fixed-effects model was used in the analysis. Table 5 presents the weighted mean reductions from baseline of SBP and DBP and BP control rate for each aliskiren/HCTZ combination commercially available. It should be noted that four RCTs were not placebo-controlled and, furthermore, the active comparator (aliskiren or HCTZ)

differed in these studies (Jordan et al., 2007; Nickenig et al., 2008; Blumenstein et al., 2009; Geiger et al., 2009). In these circumstances, appraisal of the change from baseline in SBP and DBP achieved by each aliskiren/HCTZ combination allows some appreciation of their antihypertensive efficacy since all data are derived from studies of similar design. Nevertheless, the higher BP reductions reported in the Villamil (2007) trial (Villamil et al., 2007) with aliskiren/HCTZ (a fact also observed with aliskiren and HCTZ monotherapies) must be observed with some caution, as they clearly diverged upward from the results obtained by other authors and yielded an unexpected higher effect of the lowest dose of aliskiren/HCTZ commercially available (150/12.5 mg).

Reference	Pts., n (ITT)	Treatment and daily dose (mg)	Δ in PRA from pretreatment[a] or baseline[b, c] (%)	Δ in PRC from pretreatment[a] or baseline[b,c] (%)	Adverse Events
Villamil (2007)	192 183 183 180 194 188 173 187 189 186 173 184 187 180 173	Placebo Aliskiren 75 Aliskiren 150 Aliskiren 300 HCTZ 6.25 HCTZ 12.5 HCTZ 25 Aliskiren/HCTZ 75/6.25 Aliskiren/HCTZ 75/12.5 Aliskiren/HCTZ 75/25 Aliskiren/HCTZ 150/6.25 Aliskiren/HCTZ 150/12.5 Aliskiren/HCTZ 150/25 Aliskiren/HCTZ 300/12.5 Aliskiren/HCTZ 300/25	+0.7[d] -54.2 -65.1 -57.6 +3.5 +44.7 +71.9 -54.5 NR NR NR -49.6 NR NR -62.3	+30 +164 +192 +348 +10[e] +26[e] +108 PRC increased in all combination groups and was related to dosages of both drugs. +1211	The overall incidence of treatment-related adverse events (AEs) was slightly higher in the HCTZ (9.3-11.0%) and combination groups (8.7-16.6%) compared with placebo (8.8%) and aliskiren (6.5-9.8%) groups. However, this could not be attributed to any particular AE or class of AE. Hypokalaemia (serum potassium <3.5 mmol/L) occurred with the highest frequency in HCTZ 12.5 and 25mg groups (3.9 and 5.2%, respectively). When these doses of HCTZ were administered in combination with aliskiren, the frequency of hypokalaemia decreased to 0.7–2.0% for the combination groups with HCTZ 12.5mg and to 2.2–3.4% for the combination groups with HCTZ 25mg.
Jordan (2007)	117 113 117 122	HCTZ 25 Aliskiren/HCTZ 300/25 Irbesartan/HCTZ 300/25 Amlodipine/HCTZ 10/25	+46.3[f] -45.0[f] +536.6[f] +195.6[f]	NR NR NR NR	Amlodipine/HCTZ group had the highest rate of AEs (45.2%) because of a higher incidence of peripheral edema. Incidence of AEs in the other treatment groups was: 39.3% - aliskiren/HCTZ; 38.5% – HCTZ; 36.1% - Irbesartan/HCTZ. The proportion of patients experiencing nasopharyngitis, dizziness and hyperkalaemia were slightly higher in aliskiren/HCTZ group (8.2%, 3.3% and 5.7%, respectively).
Nickenig (2008)	296 292 284	Aliskiren 300 Aliskiren/HCTZ 300/12.5 Aliskiren/HCTZ 300/25	NR NR NR	NR NR NR	Aliskiren/HCTZ SPC treatment showed similar tolerability to aliskiren monotherapy. Headache, hypercholesterolemia and nasopharyngitis occurred in ≥2% of patients in any treatment group. The proportion of patients with hypokalaemia was lower in the aliskiren/HCTZ 300/12.5 mg group (0.4%) and aliskiren 300 mg monotherapy group (0.4%) than in the aliskiren/HCTZ 300/25 mg group (2.5%).

Reference	Pts., n (ITT)	Treatment and daily dose (mg)	Δ in PRA from pretreatment[a] or baseline[b, c] (%)	Δ in PRC from pretreatment[a] or baseline[b,c] (%)	Adverse Events
Blumenstein (2009)	244 242 232	HCTZ 25 Aliskiren/HCTZ 150/25 Aliskiren/HCTZ 300/25	NR NR NR	NR NR NR	Aliskiren/HCTZ SPC treatment showed similar tolerability to HCTZ alone and a numerically lower incidence of hypokalaemia (aliskiren/HCTZ, 1.3-2.2%; HCTZ alone, 3.4%). AEs reported in ≥2% of patients in any treatment group were nasopharyngitis, dizziness, back pain and vertigo.
Geiger (2009)	151 164 154 168	HCTZ 25 Aliskiren/HCTZ 300/25 Valsartan/HCTZ 320/25 Aliskiren/Valsartan/HCTZ 300/320/25	-13.2[g] -40.5[h] +509.5[h] +38.9[g]	-29.1[i] +489.8[j] +561.4[j] +1760.1[j]	Aliskiren/HCTZ SPC treatment showed similar tolerability to HCT alone and a numerically lower incidence of hypokalaemia (aliskiren/HCTZ, 5.0%; HCTZ alone, 9.3%), nasopharyngitis (aliskiren/HCTZ, 3.0%; HCTZ alone, 6.6%) and headache (aliskiren/HCTZ, 2.4%; HCTZ alone, 5.3%).

[a]Jordan (2007); [b]Villamil (2007); [c]Geiger (2009); [d]P > 0.05 vs baseline; [e]P > 0.05 vs placebo; [f]P < 0.05 vs pretreatment; [g]P > 0.75 vs baseline; [h]P < 0.001 vs baseline; [i]P ≥ 0.05 vs baseline; [j]P < 0.05 vs baseline.
Abbreviations: AE, adverse event; HCTZ, hydrochlorothiazide; ITT, intention-to-treat analysis; NR, not reported; PRA, plasma renin activity; PRC, plasma renin concentration; Pts, patients; SPC, single-pill combination.

Table 6. Changes from baseline in PRA and PRC with aliskiren and HCTZ monotherapy and combination therapy

Some authors also studied changes from pre-treatment (Jordan et al., 2007) (start of single-blind treatment) or baseline (Villamil et al., 2007; Geiger et al., 2009) (start of double-blind treatment) in PRA and PRC with aliskiren and HCTZ monotherapy and combination therapy (Table 6). Aliskiren 75, 150 and 300 mg/day decreased (the geometric) PRA from baseline by 54.2%, 65.1% and 57.6%, respectively (Villamil et al., 2007). Conversely, HCTZ monotherapy significantly increased PRA at 12.5 and 25 mg/day dosages (Jordan et al., 2007; Villamil et al., 2007). When combined, aliskiren/HCTZ significantly reduced PRA from pretreatment (by 45%) (Jordan et al., 2007) and baseline (by 40.5-62.3%) (Villamil et al., 2007; Geiger et al., 2009), whereas combined treatment with amlodipine/HCTZ, irbesartan/HCTZ and valsartan/HCTZ significantly increased PRA (Jordan et al., 2007; Geiger et al., 2009). Aliskiren elevated PRC from baseline in a dose-dependent manner, with increases of 164%, 192% and 348% at dosages of 75, 150 and 300 mg/day, respectively (Villamil et al., 2007). HCTZ 25 mg/day increased PRC by 108%, whereas lower dosages did not cause alterations in PCR that significantly differed from placebo. All aliskiren/HCTZ combinations significantly increased PCR (Villamil et al., 2007; Geiger et al., 2009), the magnitude of increases was related to the dosages of both components, with the most marked increase (1211% from baseline) occurring in the aliskiren/HCTZ 300/25 mg group (Villamil et al., 2007). Furthermore, increases in PRC in several combination groups were considerably greater than the sum of the increases seen with each component (Villamil et al., 2007). It should be noted that Geiger *et al* measured the baseline PRA and PCR at the end of

the 4-week single-blind HCTZ period (Geiger et al., 2009). Therefore, the effect of HCTZ on PRA and PRC might have been stabilized with this initial therapy and no further changes after the 8-week additional HCTZ treatment was observed (Geiger et al., 2009).

Table 6 also describes the most common adverse events reported in the clinical trials. Aliskiren/HCTZ, as a SPC or as a combination of the individual components concurrently administered, was generally well tolerated in the five clinical trials reviewed. The majority of adverse events were mild and transient in nature, with the most commonly reported events including nasopharyngitis (Jordan et al., 2007; Villamil et al., 2007; Nickenig et al., 2008; Blumenstein et al., 2009; Geiger et al., 2009), headache (Jordan et al., 2007; Villamil et al., 2007; Nickenig et al., 2008; Blumenstein et al., 2009; Geiger et al., 2009), dizziness (Jordan et al., 2007; Blumenstein et al., 2009), back pain (Blumenstein et al., 2009), vertigo (Blumenstein et al., 2009) and hypercholesterolemia (Nickenig et al., 2008).

The proportion of patients experiencing hypokalaemia (defined as serum potassium levels <3.5 mmol/L) were numerically lower with aliskiren/HCTZ than with HCTZ alone (Villamil et al., 2007; Blumenstein et al., 2009; Geiger et al., 2009). The proportion of patients with hypokalaemia was also lower in the aliskiren/HCTZ 300/12.5 mg group (0.4%) and aliskiren 300 mg monotherapy group (0.4%) than in the aliskiren/HCTZ 300/25 mg group (2.5%) (Nickenig et al., 2008). In obese hypertensive patients, hypokalaemia occurred in 4.9% patients of the aliskiren/HCTZ group versus 2.5%, 10.3% and 4.1% of patients treated with irbesartan/HCTZ, amlodipine/HCTZ or HCTZ alone, respectively (Jordan et al., 2007).

6. Discussion

SPCs of aliskiren/HCTZ has recently been introduced in European Union for the second-line treatment of adults with essential hypertension whose BP is not adequately controlled with either drug alone, or as a substitution treatment in patients with hypertension adequately treated by the two individual drugs concomitantly at the equivalent fixed dosage. To our knowledge, this study represents the first published meta-analytical approach to the efficacy of aliskiren/HCTZ in reducing BP in patients with mild to moderate hypertension. Although other reviews dealing with the same topic are available in the literature, no study has provided a synthesis of data from clinical trials.

The five studies included in this systematic review are short-term (8-12 weeks) randomized, double-blind, clinical trials with a similar design and comparable primary endpoints and secondary efficacy measures. All studies compared the change in SBP and DBP from baseline (start of double-blind treatment) to week 8 endpoint in each aliskiren/HCTZ combination group with that in placebo and/or aliskiren monotherapy and/or HCTZ monotherapy group. Patient demographics and baseline characteristics were also similar across treatment groups in all included studies, except that one study included obese patients only (Jordan et al., 2007). The average quality of the articles was considered to be very good.

In this study we chose to present the results by way of weighted average sums of BP reductions over 8 weeks, a period consistent with current clinical recommendations for assessing the clinical efficacy and tolerability of antihypertensive drugs following their initiation (Chobanian et al., 2003; Mancia et al., 2007). The weighted means method, which has been used in other meta-analyses (Conlin et al., 2000; Baguet et al., 2005; Baguet et al.,

2007), takes into account the different sizes of trials and provides results that are easy to interpret clinically.

In all clinical trials selected for analysis, commercially available aliskiren/HCTZ combinations (150/12.5 mg, 150/25 mg, 300/12.5 mg and 300/25 mg) provided clinically significant additional SBP and DBP reductions and improved BP control rates over aliskiren or HCTZ monotherapy, which demonstrates that aliskiren/HCTZ SPCs are a effective treatment option for patients with mild to moderate hypertension who do not achieve BP control with aliskiren 300 mg or HCTZ 25 mg alone. A meta-analysis of 354 randomized clinical trials involving more than 40,000 treated patients with hypertension revealed that the additional reduction in BP achieved with antihypertensive combination therapy versus monotherapy provide a reduced risk of stroke and ischemic heart events (Law et al., 2003). In another meta-analysis, examining individual data from one million adults in 61 prospective studies, it was found that, at ages 40-69 years, each increase of 20 mm Hg usual SBP (or, approximately equivalently, 10 mm Hg usual DBP) is associated with more than a twofold difference in the stroke death rate, and with twofold differences in the death rates from ischaemic heart disease and from other vascular causes (Lewington et al., 2002). Thus, the additional mean BP reductions of up to 8.0/4.8 mmHg (versus HCTZ 25 mg) or 6.0/3.1 mmHg (versus aliskiren 300 mg) provided by aliskiren/HCTZ 300/25 mg in the present analysis might be expected to reduce the risk of cardiovascular mortality. However, long-term and large-scale studies analysing the effects of aliskiren/HCTZ combination therapy on clinical outcomes are required to confirm this hypothesis.

The capacity of aliskiren to enhance the antihypertensive efficacy of HCTZ reflects its complementary mode of action, targeting the RAAS at its point of activation and thus suppressing PRA. HCTZ monotherapy increased PRA, as a result of stimulated renin release in response to reduced intravascular volume. The addition of aliskiren counteracted this effect, resulting in a significant ($p < 0.05$) overall decrease in PRA compared with HCTZ monotherapy (Jordan et al., 2007; Villamil et al., 2007; Geiger et al., 2009). Furthermore, aliskiren effectively inhibited the renin enzyme, despite marked elevation in PRC, to produce an overall reduction in PRA from baseline. This contrasts to agents that block the RAAS at other points, such as ACE inhibitors and ARBs, which induce increases in PRA in parallel with PRC (Nussberger et al., 2002; Jordan et al., 2007; Geiger et al., 2009).

Aliskiren/HCTZ was generally well tolerated in the clinical trials reviewed and not associated with a notably higher incidence of adverse events than treatment with either component alone. These results are consistent with a long-term open-label study in 1955 hypertensive patients showing that aliskiren/HCTZ free combinations were well tolerated over up to 12 months of treatment (Sica et al., 2006; Gradman et al.,) 2007). In three included trials, when aliskiren and HCTZ was administered in combination, aliskiren opposed the adverse hypokalaemic effects of HCTZ (Villamil et al., 2007; Blumenstein et al., 2009; Geiger et al., 2009). The safety profile of an aliskiren/valsartan/HCTZ combination was also investigated in one clinical trial and was similar to the 2-drug combinations (aliskiren/HCTZ or valsartan/HCTZ), with a greater BP-lowering effect in patients not adequately responding to HCTZ monotherapy (Geiger et al., 2009).

Most patients with hypertension will require combination treatment with two or more antihypertensive medications in order to achieve BP control to recommended levels

(Chobanian et al., 2003; Mancia et al., 2007). A meta-analysis of adherence studies showed that the use of SPC regimens reduced the rate of non-compliance by 24–26% compared with respective free combinations (Bangalore et al., 2007). Aliskiren/HCTZ SPCs therefore offers the convenience of a single-tablet once daily treatment regimen, which may improve treatment compliance and subsequent BP control.

The limitations of this study should be noted. Firstly, the intervention effect size as reported above (Tables 2 and 3) could be an overestimate due to publication bias since the manufacturer (Novartis Pharmaceuticals Corporation) sponsored four (Jordan et al., 2007; Nickenig et al., 2008; Blumenstein et al., 2009; Geiger et al., 2009) of the included published studies and one author of the remaining study (Villamil et al., 2007) is employee of Novartis Pharmaceuticals Corporation. It is possible that less optimistic studies have not been published and therefore not included in our analysis. Secondly, because the BP lowering efficacy estimate is limited to 8 weeks, we cannot extrapolate our results to the longer term benefits of the treatments on cardiovascular morbidity and mortality. However, in this regard, the 2007 European Society of Hypertension (ESH)/European Society of Cardiology (ESC) guidelines are pertinent, which state that the size of BP reduction is more important than the class used for cardiovascular event reduction (Mancia et al., 2007). Thirdly, an overall of 87% patients included in the RCTs analysed were Caucasian, which greatly limits the extraction of conclusions for hypertensive patients of other races/ethnicities. Actually, blacks are known to have a less responsive renin-angiotensin-aldosterone system (He et al., 2001) and ACE inhibitors and angiotensin receptor antagonists are less effective in this subpopulation (Cushman et al., 2000; Brewster et al., 2004). One other limitation is based on the fact that there is only one clinical trial investigating the antihypertensive efficacy of the lowest dose of aliskiren/HCTZ commercially available (150/12.5 mg), which, additionally, lacks information on outcome variability (SEM or CI) (Villamil et al., 2007). This fact was responsible for an unexpected higher efficacy of aliskiren/HCTZ 150/12.5 mg in reducing SBP and DBP, when compared with higher combination dosages (Table 5). Further studies are required to accurately evaluate the dose-related antihypertensive efficacy of the commercially available aliskiren/HCTZ combinations.

7. Conclusion

In conclusion, aliskiren/HCTZ combinations commercially available were effective and generally well tolerated in clinical trials evaluating its antihypertensive effects in adults with mild to moderate hypertension and in hypertensive patients with obesity, providing clinically significant additional BP reductions and improved BP control rates in patients who are inadequately controlled with aliskiren or HCTZ monotherapy. The aliskiren/HCTZ SPCs present the convenience of a once-daily single-tablet treatment regimen, which may improve treatment adherence and subsequent BP control. Further studies are required to evaluate the relative benefits of the aliskiren/HCTZ SPCs with generically available alternatives. Also, long-term trials evaluating the efficacy and tolerability of this combination therapy would be of interest to establish the ultimate effects of treatment on the cardiovascular morbidity and mortality of hypertension.

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9. References

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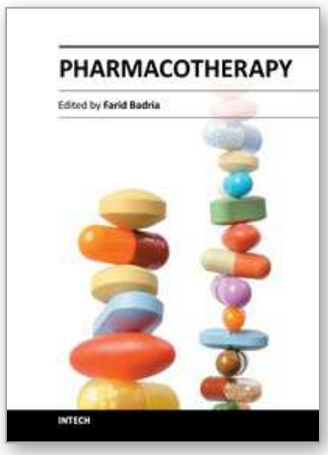

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The intent of this book is to provide an overview of current conceptualizations of Pharmacotherapy. The book focuses on three major areas; diagnosis, treatment, and prevention for a wide array of diseases; Cognitive and Psychological disorders (Schizophrenia and Nicotine addiction), Inflammatory disorders (New Chemical anti-inflammatory and Immunotherapy), updated antihypertensive therapy and healing of ulcers with venous origin. A separate chapter is dedicated to the rationality of drug use in earthquake injuries. The last chapter deals with Imaging of potential therapeutic or diagnostic agents in animal models in the early stage of research. We hope this book is useful to a wide range of people, from students first learning about Pharmacotherapy, to advanced clinicians and researchers.

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